Remarks

Applicants request entry of the amendments, consideration of the attached comments and remarks, and reexamination and allowance of the application.

Claims 1, 2 and 5 are amended. No new matter enters by the amendments. The support for the amendment to claim 1 can be found throughout the specification as a whole, and in particular at page 8, lines 10-18 of the specification, where "proteins or polypeptides" are recited. The amendments to claims 2 and 5 clarify the inhibitor referred to from claim 1 in these dependent claims.

The Office Action notes that the Information Disclosure Statement does not comply with the rules. In the Information Disclosure Statement, applicants avail themselves of the provisions allowing the documents and information submitted and cited in all the prior U.S. and PCT applications to be associated with and considered in this application. In addition, applicants submit with this Reply new forms for publication of the documents on the face of the patent. Since a new listing of the documents need not be submitted under the rules, applicants submit the new forms solely for the convenience of the Examiner. Applicants request that a confirmation that all information from the prior applications will or has been considered in this application.

The Office Action also notes the priority benefit date at page 3. However, applicants are unsure of the reasoning behind the determination of that date. The

first U.S. case, 08/737,953, was filed as a 371 application and the FR 94/06583 priority document was forwarded to the U.S. by the International Bureau. Both the parent and grandparent applications recognized this. Applicants representative will attempt to contact the Examiner to resolve any confusion.

Rejections under 35 U.S.C. § 112

Claims 2, 5-7 stand rejected under 35 U.S.C. § 112, second paragraph, as it is allegedly not clear which inhibitor these claims refer to.

Claim 1 has been amended to recite protein or peptide inhibitors and claims 2 and 5 are amended to recite "the administered inhibitor."

This rejection should now be withdrawn.

Claims 5 and 7 are rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to provide a written description of the claimed subject matter. Applicants respectfully disagree.

Applicants note that the specification specifically refers to fragments of calpastatin in SEQ ID NO: 3-4 and at page 20, line 27 to page 21, line 3. The Maki reference discussed in the specification is evidence that one of skill in the art could indeed determine what an inhibitory fragment of calpastatin was according to the invention.

As discussed below, applicants explain and show in the specification that they were the first to recognize that p53 proteins are direct substrates for calpain

enzymatic activity and that direct inhibition of the calpains can prevent the enzymatic degradation of p53. With this information, one of skill in the art could have looked for any of the known or available compounds that effect calpain enzymatic action, and the specification refers to this information generally at page 22, lines 15-20.

Accordingly, applicants submit they have adequately described the claimed invention of claims 5 and 7 by both providing examples and referring to known and available examples in the specification.

With respect to the structure of calpastatin referred to in the Office Action at page 5, the Carafoli review document, of record in this and parent case, refers to several documents at page 194 (reference numbers 32-34) that indicate that one of skill in the art did indeed possess information on the inhibitory domains in the calpastatin protein. Applicants need not specifically include what is known and available into their specification document.

Applicants request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 102

Claims 1, 2, and 8 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ramsby (Electrophoresis 1994). Applicants respectfully disagree.

Applicants note that the Ramsby document appears only to refer to the use of EDTA in preparing samples for 2-D electrophoresis and to avoid "artifactual

proteolysis" (see page 271). There does not appear to be any reason why one of skill in the art would consider this artifactual proteolysis relevant to any method to detect the direct p53 protein degradation referred to in applicants' invention. No reasons were explained in the Office Action.

In order to advance prosecution, applicants have amended claim 1 to recite a "peptide or protein" inhibitor. The specification as a whole supports these amendments. As noted above, page 8, lines 10-18 specifically refers to proteins and polypeptides and at least page 8, lines 19-26 refers to encoded inhibitors of calpain, which necessarily would be a peptide or protein and would be derived from the cellular production of peptides or proteins. The specification refers to numerous ways of administering an inhibitor of calpain using gene transfer methods and viral vectors for example, which also necessarily implicate a cell-produced peptide or protein inhibitor.

The Office Action also refers to the mention of calpastatin in the Ramsby document. However, applicants submit that a proper anticipatory reference must include each and every element of the claimed invention. Nothing within the four corners of the Ramsby document refers to administering a peptide or protein inhibitor of calpain protease activity.

For at least this reason, this rejection should be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ramsby in view of Asada (J. Enzym. Inhibit. 1989). Applicants respectfully disagree

Applicants noted above that the primary reference Ramsby refers to EDTA as an inhibitor to avoid "artifactual proteolysis" (see page 271). As one of skill in the art would clearly understand, any work relating to "artifactual proteolysis" would lead nowhere close to any aspect of the direct p53 degradation by calpain forming part of the basis for the current invention.

In addition, at page 276, the Ramsby authors set forth what they consider particularly useful assays for the 2-D gels with the added EDTA to reduce artifactual protease activity. "Specifically, we have used DDF to : (i) investigate a potential regulatory role for calpains/calpastatin and intermediate filaments in autophagic sequetration ... " (page 276, second column, second paragraph). Nowhere is any mention of an assay or method for p53 referred to in the Office Action's reasoning based upon the Ramsby document. The number of potential proteins that one could have identified by 2-D gels from the proteins of liver cells used in Ramsby is quite large. It is unclear if the Office Action posits that each and every one of those proteins, and perhaps all the undisclosed fragments of each of these proteins, is inherently being assayed in the methods of Ramsby.

Accordingly, since Ramsby neither identifies a reason to specifically consider p53 degradation by calpain nor does it suggest a reason to administer a

peptide or protein inhibitor of calpain protease activity, the document fails to teach or suggest the claimed invention of claim 1 and its dependent claims.

The addition of the Asada document, which is cited for the human calpastatin sequences it discusses, does not address the deficiencies in the primary reference noted above.

The Office Action suggests that it would have been obvious to substitute one known element for another to result in predictable results (see page 10). However, the Office Action asserts that the Ramsby document teaches calpastatin in some specific way relevant to the claimed invention. The Ramsby document, as stated in the Office Action, discusses the use of EDTA but as a preventative measure to avoid "artifactual proteolysis." Any suggestion that Ramsby even suggests any specific protein or peptide inhibitor as being used for the purpose of inhibiting p53 protein degradation is purely hindsight analysis. One of skill in the art might consider Ramsby as suggesting that every known protease inhibitor should be used in the 2-D samples in order to preserve the largest fraction of proteins for the potential assays noted. That one specific class of inhibitors should be used for one specific protein is nowhere mentioned.

In fact, one of skill in the art would consider it clear that the focus of Ramsby is on preservation of the samples in order to dissect the partitioning of proteins into subcellular components. Ramsby notes this as the "differential detergent fractionation" method throughout the document. The use of 2-D gels to look for

proteins is a very general approach and has nothing to do with the specific methods claimed here.

Having fully responded to the Office Action and shown that the application is now in condition for allowance, applicants request prompt notice of allowance.

If there are any fees due with the filing of this paper not accounted for, applicants respectfully request that any and all fees be charged to Deposit Account No. 50-1129, with reference to matter no. 80375.0033. If any extension of time request or any petition is required for the entry of this paper, applicants hereby request the extension necessary. The undersigned authorizes the extension fee payment, as well as any other fee payment necessary or missing or not accounted for, from Deposit Account No. 50-1129, with reference to matter no. 80375.0033.

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Respectfully submitted,

By: _____
David J. Kulik, Esq.
Reg. No. 36,576
Heather Ramirez
Reg. No. 57,369

WILEY REIN LLP
Attn: Patent Administration
1776 K Street, N.W.
Washington, D.C. 20006
Telephone: 202.719.7000
Facsimile: 202.719.7049

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